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09/147,693	02/17/99	LUBITZ W	P564-9005

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1636	9

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Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/147,693	Applicant(s) Lubitz et al.
	Examiner WILLIAM SANDALS	Group Art Unit 1636

☒ Responsive to communication(s) filed on *May 31, 2000*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *38-76* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☒ Claim(s) *49* is/are allowed.

☒ Claim(s) *38-48 and 50-76* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Response to Arguments

1. Arguments in set forth in Paper No. 8, filed May 31, 2000 with respect to claims 38-48, 50-62 and 73-76 rejected under 35 USC 103(a) in the previous office action have been considered but are moot in view of the new ground(s) of rejection.

2. Arguments filed in Paper No. 8 regarding the rejection of claims 63-65, 71 and 72 under 35 USC 112, first paragraph have been fully considered and are persuasive, and the rejection is withdrawn.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 38-41, 44-46, 50-53, 55-57, 60-62, 73, 75 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Chen et al.

Chen et al. taught (see especially the summary, introduction, materials and methods and the figures) a method for selecting OR or OL operator DNA sequences from lambda phage where the operator sequences have a different thermostability as compared to wild-type operator

sequences. The operator sequences are operatively linked to an expression cassette in a plasmid which contains a selection gene (which may be a suicide gene) and a promoter. The operator sequences are subjected to mutagenesis. The repressor which binds to the operator sequences may be cI857.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 38-42, 44-48, 50-62, 66-70 and 73-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. in view of Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190.

The claims are drawn to a method for selecting mutated O_R or O_L operator DNA sequences from lambdoid phages which have different thermostability compared to wild-type sequence with regard to binding a repressor wherein the operator DNA sequence is subjected to mutation and selected for different thermostability from the wild type with respect to binding of a repressor. The repressor may be cI857, and the thermostability may be increased from 3-10° or 7-9°. The claims are also drawn to the mutated O_R or O_L operator DNA sequences from lambdoid phages which may be incorporated into a vector, and to a host bacterial cell.

Chen et al. taught the invention as described in the above rejection.

Chen et al. did not teach that the suicide gene was from PhiX174, nor that a mutator strain of bacteria may be used to induce mutations in the operator sequence, nor the specific temperature ranges of changes in the thermostability of the operator binding repressor, nor that the vector was a bacterial chromosomal vector, nor that the use of multiple operator sequences.

Eliason et al. taught (see especially the abstract, the introduction, page 2342-43 and the tables and figures) a method for selecting mutated O_R or O_L operator DNA sequences from lambdoid phages which have different binding compared to wild-type sequence with regard to binding a repressor wherein the operator DNA sequence is subjected to mutation and selected for different binding from the wild type with respect to binding of a repressor. Eliason et al. also taught mutated O_R or O_L operator DNA sequences from lambdoid phages which may be incorporated into a vector, and to a host bacterial cell.

Pakula et al. taught (see especially the abstract, introduction and the discussion) the change in thermal stability of a mutated repressor protein with the lambda operator. Pakula et al. discuss in great detail, the importance of the contact bases in the operator, and the manner in which they interact with the amino acids of the repressor protein. From their discussion, it is clear that the increased thermal stability of the binding of the repressor protein is directly related to the thermodynamics of the molecular interaction between the contact bases of the operator DNA sequence and the contact amino acids of the repressor protein. Pakula et al. taught that one

of skill in the art would be able to select mutated sequences in the repressor protein which would have greater binding affinity for the operator sequences and therefore higher thermostability.

Benson et al. taught (see especially the abstract, the introduction, page 26, column 1, and Page 28, column 1) the relative affinity of the lambda repressor protein for the lambda operator sequence, where the operator sequence has been mutated. Benson et al. show that the operator sequence was mutated to produce a mutant operator sequence which has greater affinity for the lambda repressor protein than the wild type operator sequence.

US Pat No. 4,634,678 taught (see especially the abstract, summary and the claims) the use of two or more operator sequences which have different affinities for the cI857 repressor in a single construct to produce different affinities for the cI857 repressor.

US Pat No. 5,576,190 taught (see especially the abstract, summary and column 10) the mutation of OL operator sequences to increase the binding affinity of the cI857 repressor protein.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant invention to combine the mutated DNA lambda operator sequences of Chen et al., Eliason et al. or Benson et al. with the increased thermostability of repressor sequences of Pakula et al. since Pakula et al. taught the increased thermostability of the repressor complex was due to changes in the thermodynamic molecular interaction of specific bases and amino acids in the binding site of the operator/repressor pair. US Pat No. 4,634,678 and US Pat No. 5,576,190 each taught the use of a mutated operator sequence to increase the affinity of the repressor for the operator sequence. Eliason et al. taught the changes in the operator sequence would affect the

thermodynamic stability of the interaction of the operator/repressor complex. Since cI857 is a known mutant repressor of the lambda operator, and mutations of the sequence of the cI857 would also be affected by the same thermodynamic laws which apply to the repressor/operator complexes of Chen et al., Eliason et al., US Pat No. 4,634,678, US Pat No. 5,576,190 and Pakula et al., it would have also been obvious to practice the invention with cI857.

One of ordinary skill in the art would have been motivated at the time of filing of the instant invention to combine the mutated DNA lambda operator sequences of combine the mutated DNA lambda operator sequences of Chen et al., Eliason et al. or Benson et al. with the increased thermostability of operator/repressor binding of Pakula et al. since Pakula et al. taught in the abstract that "two suppressor substitutions increase the thermal stability of Cro by 12° C to 14° C.", and in the introduction, "two substitutions that dramatically increase the thermal stability" of the repressor complex was due to changes in the thermodynamic molecular interaction of specific bases and amino acids in the binding site of the operator/repressor pair (see especially figure 4). US Pat No. 4,634,678 and US Pat No. 5,576,190 each taught the use of a mutated operator sequence to increase the affinity of the repressor for the operator sequence. Eliason et al. taught in the abstract and in the introduction that the changes in the operator sequence would affect the thermodynamic stability of the interaction of the operator/repressor complex. Since cI857 is a known repressor mutant of the lambda operator, and mutations of the sequence of the cI857 would also be affected by the same thermodynamic laws which apply to the repressor/operator complexes of Eliason et al. and Pakula et al., it would have also been

obvious to practice the invention with cI857. Benson et al. taught at page 28, "[f]rom our analysis of symmetric operators, we can rank changes in the natural operators as being severely detrimental, mildly detrimental, neutral, or beneficial for the binding of repressor". The teachings of Eliason et al. that mutation of the operator causes a change in the binding temperature of the lambda repressor to the lambda operator is confirmed and strengthened by the teachings of Benson et al. on the effects of mutation of the lambda operator in the binding affinity of the lambda repressor with the lambda operator. This makes it obvious to one of skill in the art that mutations in the lambda operator sequence would affect the temperature of activation of the lambda repressor by changing the affinity of the lambda repressor for the lambda operator. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Chen et al. in view of Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190.

7. Claim 43 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. in view of Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190. as applied to claim 38-42, 44-48, 50-62, 66-70 and 73-76 above, and further in view of US Pat No. 5,811,093.

The claims are drawn as described above and to method of use of a mutator bacterial strain to carry out the mutagenesis of the lambda operator sequence.

US Pat No. 5,811,093 taught (see especially the abstract, summary and columns 18-19) a mutator bacterial strain used for the well known mutation of a desired sequence of phage DNA.

It would have been obvious to one of ordinary skill in the art at the time of filing of the instant claimed invention to use a mutator strain of bacteria such as the mutator strain of US Pat No. 5,811,093 because of the well known use of such a strain of bacteria to produce mutations in a selected DNA sequence such as the instant claimed lambda operator sequence.

One of ordinary skill in the art would have been motivated at the time of filing of the instant claimed invention to use a mutator strain of bacteria such as the mutator strain of US Pat No. 5,811,093 because it was well known to those of ordinary skill in the art that a mutator strain of bacteria would produce the desired mutations in a selected sequence of DNA such as the instant claimed lambda operator sequence. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of unpatentable over Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190. and further with US Pat No. 5,811,093.

8. ***Response to Arguments***

Arguments set forth in Paper No. 8 assert that Eliason et al. does not teach the increase in thermostability of the cI857 repressor for the mutated operator sequences. Eliason et al. taught that the mutated operator sequences have a higher affinity for the cI857 repressor. Pakula et al. taught the thermodynamics of the interaction of a repressor with mutated operator sequences. Pakula et al. make it very clear that an increase in affinity of the repressor for the operator

sequences will also increase the thermostability of the repressor as it binds to the mutated operator sequences.

Arguments set forth in Paper No. 8 assert that Pakula et al. and Benson et al. do not teach the cI857 repressor. The teachings of Pakula et al. and Benson et al. are used to demonstrate features of the invention which are clearly relevant to the teachings of the primary reference, and make obvious the instant invention.

9. Claims 63-65, 71 and 72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 as applied to claims 38-42, 44-48, 50-62, 66-70 and 73-76 above, and further in view of Szostak et al

The claims are as described in the rejection above and to a vaccine composition comprising the bacterial cell and bacterial cell ghosts produced by transfecting bacterial cells with the above claimed compositions and methods.

Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 did not teach the vaccine composition comprising the bacterial cell and bacterial cell ghosts produced by transfecting bacterial cells with the above claimed compositions and methods.

Szostak et al. taught (see especially the abstract, materials and methods and the figures) vaccines made by transfecting bacterial cells with the above claimed compositions and methods.

It would have been obvious to one of ordinary skill in the art at the time of filing the instant claimed invention to combine the composition comprising the transfecting of bacterial cells with the above claimed compositions and methods of Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 with the vaccine composition comprising the bacterial cell and bacterial cell ghosts of Szostak et al. because Szostak et al. used the bacterial cells transfected with the above claimed compositions and methods to make vaccines with bacteria and bacterial ghosts according the instant claimed invention. Szostak et al. state at page 424 "[g]eneration of humoral and cellular immune responses by bacterial ghosts carrying RT-specific fusion proteins in the cell envelope indicates that this approach of immunostimulation by carrier cells and targeting antigens might be useful in the development of candidate vaccines. As the immune response is directed against the carrier and the membrane, targeted fusion protein combination vaccines can be envisaged." These comments make it clear, combined with the success of producing an immunized animal with the bacterial cell ghosts, that it would have been obvious to combine the teachings of the vectors of Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 and Szostak et al to produce the instant claimed vaccine compositions. Further, a person of ordinary skill in the art would have had a reasonable expectation of success in the producing the instant claimed invention given the teachings of Chen et al. with Eliason et al., Pakula et al., Benson et al., US Pat No. 4,634,678 and US Pat No. 5,576,190 and Szostak et al.

Allowable Subject Matter

10. Claim 49 is allowed.

Conclusion

11. Certain papers related to this application are ***welcomed*** to be submitted to Art Unit 1636 by facsimile transmission. The FAX numbers are (703) 308-4242 and 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by the applicant or applicant's representative, and the FAX receipt from your FAX machine is proof of delivery. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications should be directed to Dr. William Sandals whose telephone number is (703) 305-1982. The examiner normally can be reached Monday through Friday from 8:30 AM to 5:00 PM, EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott can be reached at (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group Receptionist, whose telephone number is (703) 308-0196.

William Sandals, Ph.D.
Examiner
August 11, 2000

George C. Elliott, Ph.D.
Supervisory Patent Examiner
Technology Center 1600